NATIONAL ASSOCIATION
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May 4, 2004

Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket number 200D-1350, "Draft Guidance for Industry on Labeling for Combined Oral Contraceptives"

Dear Sir/Madam:

The National Association of Nurse Practitioners in Women's Health (NPWH) was founded in 1980. NPWH's mission is to assure the provision of quality heath care to women of all ages by nurse practitioners. The nurse practitioners represented by NPWH both recommend and prescribe oral contraceptives. We are commenting on the Draft Guidance for Industry on Labeling for Combined Oral Contraceptives.

Comments by Select Topics

Precautions – General (pg. 8, lines 286-292)

The draft guidance recommends that women using oral contraceptives have an annual history and physical examination, with specific reference to pelvic organs and cervical cytology. This recommendation, however, is not supported by the available medical literature and is inconsistent with the guidelines of leading national and international medical and health organizations. Indeed, the United States Agency for International Development,[1] the World Health Organization,[2] the International Planned Parenthood Federation,[3] the American College of Obstetricians and Gynecologists,[4] the

[1] World Health Organization and U.S. Agency for International Development. *Recommendations for Updating Selected Practices in Contraceptive Use, Volume I.* Washington, DC: WHO and USAID; 1994.
[2] *ibid.*
[3] International Planned Parenthood Federation. IMAP statement on steroidal oral contraception. *IPPF Med Bull.* 1995:29;1-6.
[4] American College of Obstetricians and Gynecologisits. *Guidelines for Women's Health Care,* Washington, DC: 1996.

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Society of Obstetricians and Gynaecologists of Canada,[5] the Royal College of Obstetricians and Gynaecologists,[6] and the American Academy of Pediatrics[7] as well as NPWH all conclude that pelvic examinations are not necessary prior to the initiation of oral contraceptives, even among adolescents.

Furthermore, the Food and Drug Administration's (FDA) own oral contraceptive labeling documents has recognized this evolution of thought. The 1994 guidance states that, "the physical examination ... may be deferred until after initiation of oral contraceptives if requested by the woman and judged appropriate by the clinician."[8] This was later refined in the draft guidance made available in 2000: "Before initiating COC use, blood pressure should be measured and details of the woman's personal and family medical history should be obtained. Blood pressure should be measured periodically during COC use and additional clinical evaluation should be based on these initial and follow-up findings."[9]

Blood pressure assessment is the only portion of the recommended physical examination that is relevant to use of COCs as hypertension is a contraindication to use of this method. An annual physical examination with specific reference to the pelvic organs, as well as cervical cytology, is simply inconsistent with current medical practice. Women at low risk for cervical cancer with three prior negative screening tests for cervical dysplasia can reduce the frequency of their cervical cancer screening to every two to three years. The FDA's proposed labeling requirement, should it stand, would be at odds with current medical professional recommendations.

The statements of the aforementioned medical and health organizations, including the FDA, represent an evolution in both our understanding of hormonal contraceptives as well as the composition of the oral contraceptives (OC) themselves. When OCs were first available, it was prudent to require a physical examination, including a pelvic examination. As the body of medical and scientific literature grew and enhanced our understanding of hormonal contraceptives, and as the amount of hormone in each pill decreased, the necessity of a physical examination, and a pelvic examination in

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[5] Society of Obstetricians and Gynaecologists of Canada. The Canadian Consensus Conference on Contraception. Toronto: Society of Obstetricians and Gynaecologists of Canada; 1998. Available at: http//sogs.medical.org/SOGCnet/sogc_docs/common/guide/library_e.shtml. Reprinted from: *JSOGC*:1998:20.

[6] Faculty of Family Planning and Reproductive Health Care, Royal College of Obstetricians and Gynaecologists. First prescription of combined oral contraception: recommendations for clinical practice. *Br J Fam Plann.* 2000;26:27-38.

[7] Committee on Adolescence. American Academy of Pediatrics. *Contraception and Adolescents.* Pediatrics Vol. 104 No. 5, November 1999.

[8] Labeling Guidance for Combination Oral Contracpetives, Food and Drug Administration. Page 12. August 1994.

[9]

particular, was questioned. Eventually, medical and health organizations arrived at positions that decoupled the pelvic examination from initiation of OCs/COCs.

Additionally, as providers of family planning services, it has become apparent to us that the requirement of a pelvic examination prior to initiation of OCs/COCs often serves as barrier to contraception. Adolescents, in particular, are likely to avoid or delay initiation of contraception because of reluctance to undergo a pelvic examination. Because women's health is in no way compromised by delaying a pelvic examination when initiating OCs, NPWH believes that women are better served by eliminating this unnecessary requirement.

Finally, it is worth noting that Ortho Tri-Cyclen is also indicated for treatment of moderate acne vulgaris in females $\geq$ 15 years of age.[10] Women who are prescribed this COC for treatment of acne should certainly not be required to undergo a pelvic examination prior to initiation of treatment. Labeling that requires providers to perform a pelvic examination would be inconsistent with the use of this product for treatment of acne.

Given that there is no medical justification for requiring a pelvic examination prior to initiation of COCs, and that requiring such an examination has been shown to serve as a barrier to contraception, NPWH urges the FDA to reconsider its labeling guidance and omit the requirement for a pelvic examination from the final industry guidance document.

Precautions – Nursing Mothers (pg. 10, lines 386-391)

The 2004 draft guidance recommends that, if possible, nursing mothers be advised to use other forms of contraception until her child has been weaned. This recommendation differs significantly from the previously published draft guidance (2000), which states that, "women who are fully breast-feeding should not start taking COCs until 6 weeks postpartum."[11]

Although contraceptives containing both estrogen and progestin have been shown to reduce both the quantity and quality of breast milk, by delaying COC initiation until 6 weeks postpartum, sufficient time is allowed for establishing breastfeeding techniques and skills. These techniques and skills, in turn, can mitigate against any decrease in milk quality or quantity that may result from COC initiation.

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[10] Ortho Tri-Cyclen Tablets Prescribing Information. Ortho-McNeil Pharmaceutical, Inc. Raritan, NJ; revised March 2001.

[11]

Absent medical evidence to the contrary, NPWH recommends that the FDA retain the earlier language that advises women to delay initiation of COCs until 6 weeks postpartum. This recommendation allows women who elect to contracept using COCs to protect themselves against an unintended pregnancy while continuing to breastfeed their infants. Furthermore, this recommendation is supported by a World Health Organization study that found that infant growth was not affected by impaired milk secretion.[12]

Possible Health Benefits (page 11, lines 431-438)

NPWH believes that the list of non-contraceptive health benefits that accrue to pill users is too meager. The benefits indicated in the 2004 draft guidance relate specifically to menses and do not include the therapeutic implications of these benefits. The effects of consistent OC use on estrogen and progestin sensitive tissues and organs have been shown to result in non-contraceptive health benefits that form the basis for therapeutic uses of oral contraceptives in instances of dysfunctional uterine bleeding, iron-deficiency anemia associated with menorrhagia, hypothalamic amenorrhea with associated osteoporosis, dysmenorrhea, mittelschmerz, polycystic ovarian syndrome, acne, and recurrent, functional ovarian cysts.[13] In addition, consistent use of COCs provides protection against pelvic inflammatory disease,[14] reduces the incidence and prevalence of benign breast disease, helps prevent osteoporosis,[15,16] and significantly reduces the lifetime risks of endometrial[17,18] and ovarian cancers.[19,20,21,22] Moreover,

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[12] Tankeyoon M, Dusitsin N, Chalapti S et al. Effects of hormonal contraceptives on milk volume and infant growth. Contraception 1984;30(6):505-22.

[13] (Mishell DR jr. Non contraceptive Health benefits of oral steroidal contraceptives. Am j Obstet Gynecol. 1982;142:809-----we will need to find the primary reference for this from Mishell's article).

[14] (Mishell DR jr. Non contraceptive Health benefits of oral steroidal contraceptives. Am j Obstet Gynecol. 1982;142:809-----we will need to find the primary reference for this from Mishell's article),

[15] (Mishell DR jr. Non contraceptive Health benefits of oral steroidal contraceptives. Am j Obstet Gynecol. 1982;142:809-----we will need to find the primary reference for this from Mishell's article),

[16] Kost K, Forrest JD, Harlap S. Comparing the health risks and benefits of contraceptive choices. Fam Plann Perspec. 1991;23:54-61---also need primary reference)

[17] CDC/NICHD. Oral contraceptives and endometrial cancer: combination oral contraceptive use and the risk of endometrial cancer. JAMA. 1987;257:6

[18] The Centers for Disease Control Cancer and Steroid Hormone Study. Oral contraceptives and risk of endometrial cancer. JAMA. 1983;249: 1600-4

[19] The Center for Disease Control Cancer and Steroid Hormonal Study. Oral contraceptives and risk of ovarian cancer. JAMA 1983;249:1596-9

[20] Sanderson M, Williams MA, Weiss NS, et al. Oral contraceptive and epithelial ovarian cancer: does dose matter? J Reprod Med 2000;45: 720-6

[21] Siskind V, Green A, Bain C, Purdie D. Beyond ovulation: oral contraceptives and epithelial ovarian cancer. Epidemiology. 2000;11:106-110

[22] La Vecchia C, Franceschi S. Oral Contraceptives and ovarian cancer. European J Cancer Prev. 1999;8:297-304---obtain primary references

many women are attracted to the opportunity to delay menses when COCs are used continuously, without a hormone-free interval.[23]

How Do I Take (OC Name)? (pgs. 14-15, lines 508-537) and What Should I Do If I Miss Any Birth Control Pills? (pg. 15, lines 539-563)

The information provided in the most recent draft labeling guidance is insufficient and does not provide women with their full range of options with respect to initiating COCs. Oral contraceptives may be initiated at anytime during the woman's menstrual cycle, once it has been established that she is not pregnant. This information, including the full range of options and explicit examples, should be conveyed. The guidance to "talk with your health care provider about when to start your birth control pill" should also be maintained.

In addition to expanding the options available to women regarding when to initiate COCs, an expanded discussion of the options available to women to ensure adequate contraceptive protection when one or more pills have been missed should also be included in this section.

NPWH recommends the following instructions regarding COC initiation and how to ensure adequate contraceptive protection when one or more pills have been missed:

> The first dose can be taken on any day, as long as pregnancy and recent unprotected intercourse are ruled out (Quick start references and others). If more than 5 days since start of menstrual bleeding or neither postpartum nor post abortion, back-up contraception (such as condoms) is recommended for 7 days. For most women, a Sunday start translates into no menses on weekends.

- If the woman misses 1 pill, she should take it as soon as he remembers. If she does not remember until the next day, she should take 2 pills the next day, and complete the cycle pack.
- If she misses 2 consecutive pills, she should:
    - A. Take 2 pills the day she remembers and 2 pills the following day, and complete the cycle pack.
    - B. Use a back-up method for 7 days
- If she misses more than 2 consecutive pills, the risk of unplanned pregnancy may be substantial. She should:

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[23] Anderson FD, Hait H. A multicenter, randomized study of an extended-cycle oral contraceptive. Contraception 2003; 68:89-96.

- A. Stop taking the daily pills and use Emergency Contraception. Her period should begin within 2-3 weeks, unless she is pregnant.
- B. Begin a new package of pills on the Sunday after her period begins.
- C. Use a back-up method of birth control (such as condoms) from the time the error was discovered until the 8th day of the new package of pills.

Contraindications (pg. 4, lines 103-121)

Listed among the contraindications to COC use is "migraine with focal neurological symptoms." NPWH believes that this contraindication lacks specificity and should be refined to reflect current scientific findings regarding the association between migraine headaches and increased risk of ischemic stroke.

Specifically, the increased risk of ischemic stroke among women using COCs is found among those experience "migraine with aura." The contraindication listed should therefore be migraine with aura - with aura defined as specific focal neurological symptoms which usually precede and resolve before onset of migraine headache.[24,25,26,27,28,29,30]

Approximately 70 per cent of migraine sufferers experience migraine without aura. It is therefore crucial that the specific diagnosis of aura is accurately determined as those who experience migraine without aura are candidates for oral contraceptives. Aura's specific focal neurological deficits are primarily visual (99% of auras)[31] and are characterized by a bright spot which may increase in size to the shape of a letter "C" with development of scintillating edges that appear as "zigzags". These visual changes generally start centrally and then gradually spread laterally, with the size of the bright blind spot increasing over a period of 5 to 60 minutes. Generally, the aura precedes and

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[24] MacGregor EA, Guillebaud J. Recommendations for clinical practice. Combined oral contraceptives, migraine and ischaemic stroke. Br J Family Planning 1998;24:55-60.
[25] Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia 1988;8 (suppl 7):1-96.
[26] Collaborative Group for the Study of Stroke in Young Women. Oral contraceptives and stroke in young women: associated risk factors. JAMA 1975;231:718-22.
[27] Lidegaard Ø. Oral contraceptives, pregnancy and the risk of cerebral thromboembolism: the influence of diabetes, hypertension, migraine and previous thrombotic disease. Br J Obstet Gynecol 1995;102:153-9.
[28] Tzourio C, Tehindrazanarivelo A, Iglésias S, Alpérovitch A, Chedru F et al. Case-control of migraine and risk of ischaemic stroke in young women. Br Med J 1995;310:830-3.
[29] Chang CL, Donaghy M, Poulter N and World Health Organisation Collaboration Study of Cardiovascular Disease and Steroid Hormone Contraception. Migraine and stroke in young women: case-control study. Br Med J 1999;318:13-8.
[30] Becker WJ. Use of oral contraceptives in patients with migraine. Neurology 1999;53 (suppl 1):S19-S25.
[31] Russell MB, Olesen J. A nosographic analysis of the migraine aura in a general population. Brain 1996;119:355-61.

resolves before the onset of a migraine headache; occasionally, though, aura may occur without headache. Sensory or motor symptoms occur in association with one third of visual auras. When sensory motor symptoms occur they are usually unilateral in distribution, affecting one arm, the mouth and tongue, and rarely affecting the legs.[32]

Consistent with these data, the most recent update of the World Health Organization's Medical Eligibility Criteria for Contraceptive Use (third edition, in publication) will reflect the terminology "migraine with aura" rather than "migraine with focal neurological symptoms" (http://www.who.int/reproductivehealth/publications/MEC_3/summary_tables.html).

NPWH further recommends that the Warnings section of the most recent draft guidance document (page 4, lines 123-134) indicate that COCs may be used in women experiencing migraine without aura, and who have risk factors for ischemic stroke (age 35 and older; diabetes mellitus, close family history of arterial disease under 45 years, hyperlipidemia, hypertension, obesity, and smoking) other than COC use.[33,34] Use of COCs among this population, however, should be cautious. To maintain consistency with the above recommendation, "Severe migraine headache" found on page 16, line 582, of the draft guidance should be changed to read "Migraine headaches with aura."

Drug Interactions: Anti-infective agents and anticonvulsants (pg. 8, lines 307-313) and What Else Should I know About Taking (OC Name)? (pg. 17, lines 623-628)

As currently drafted, the language in this section is confusing. Providers and patients alike are left with the impression that most antibiotics, if not all, are contraindicated among COC users. The World Health Organization's *Medical Eligibility Criteria for Contraceptive Use, Third Edition* (http://www.who.int/reproductive-health/publications/MEC_3/ summary_tables.html), however, indicates that OCs are contraindicated only for users of rifampin and, in some cases, griseofulvin. There are no restrictions for use of COCs with other antibiotics. Unfortunately, the FDA's draft guidance is not clear on this point, particularly in the latter section referenced above.

NPWH suggests that the language be refined to clarify which specific antibiotics preclude use of COCs. Additionally, the revised language should make explicit the fact that antibiotics other than rifampin and griseofulvin are not contraindicated. Finally, this language should be reflected in both the package insert and the patient labeling.

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[32] *op cit* MacGregor EA, Guillebaud J.
[33] *op cit* MacGregor EA, Guillebaud J.
[34] Becker WJ. Use of oral contraceptives in patients with migraine. Neurology 1999;53 (suppl 1):S19-S25

Line 90: Table of method effectiveness rates

The table of method effectiveness rates is an important tool for women, and no doubt many health professionals as well, in comparing various methods. In that light, it is disappointing that the March 2004 guidance for industry on labeling includes a table that is significantly reduced from that which appears in the current labeling, as well as in the draft guidance published in the *Federal Register* on July 10, 2000. Information that is both pertinent and useful has been removed. We recommend that the full scope of information contained in both the current table of method effectiveness and the 2000 draft guidance be retained in the final document. However, we also recognize that the the information in the present OC label effectiveness table is not peer reviewed. Peer review of this table and methodology would increase its validity.

Of particular concern is the fact that the truncated March 2004 table presents a conflation of "perfect-use" and "typical-use" effectiveness rates for different methods. For the pill, patch and vaginal ring, the table presents "perfect-use" rates of about 1%, while for the condom, diaphragm and spermicides, it presents "typical-use" rates of 15–25%. This is a significant distortion of the effectiveness of the latter methods, all of which have "perfect-use" failure rates of 5–6% according to Hatcher et al.'s *Contraceptive Technology*. We believe that both the perfect-use and typical-use effectiveness rates should be presented for every method. Women need to be informed about what can be achieved with perfect use so that they can determine for themselves their ability to comply with a particular contraceptive regimen.

COC Use as Emergency Contraception

The FDA has acknowledged that eighteen brands of COCs can be used safely and effectively as emergency contraception (EC) after unprotected intercourse.[35] The 2000 Guidance reflected this position and included information in the labeling for healthcare providers on the use of COCs as EC; however, with the change in the effectiveness table on line 90 of the 2004 Guidance, this information has been removed. We would like to see this information reinstated in some form and believe it should also be included in the patient labeling. Incorporating this information in the labels of relevant formulations of COCs would increase provider and patient awareness of the use of COCs as EC and could prevent pregnancies after unprotected intercourse.

Herbal Products (pg. 8, lines 324-328)

[35] Food and Drug Administration. Prescription drug products: certain combined oral contraceptives for use as postcoital emergency contraception. Federal Register 1997; 62:8610-2.

With the rising popularity of St. John's Wort, there now exists some evidence that women taking this product while using COCs may experience break through bleeding. There is no evidence, however, that these same women are at risk for increased contraceptive failure. Given this lack of evidence, NPWH recommends that draft guidance be changed to reflect accurately the current body of knowledge. We suggest that lines 327-328 read as follows: ". . . p-glycoprotein transporter and may *result in breakthrough bleeding. To date, there is no evidence of increased oral contraceptive failure rates.*"[36]

Increased Cervical Ectopia (pg. 10, line 417)

There is no evidence to suggest that OCs/COCs increase a woman's risk for cervical ectopia (congenital displacement or malposition of any organ or part of the body). While there is evidence indicating that women on OCs may be at increased risk for developing increased cervical ectropion (a rolling outward or eversion of the margin of a part, i.e., eversion of endocervical glandular epithelium), this is not a pathological state and, in and of itself, cervical ectropion does not cause symptoms. Line 417 should therefore be deleted from the "Adverse Experiences" section of the draft guidance document.

Conclusion

Each year, thousands of health care providers prescribe millions of cycles of COCs to millions of women in the United States. It is imperative that the package insert and patient labeling that accompanies each cycle of COCs be complete, accurate, and clear. Only then will providers be able to make sound medical recommendations and women be provided with the tools necessary to make informed decisions. As an organization representing thousands of nurse practitioners who care for women, NPWH is obligated to our membership provide you with our comments regarding the FDA's draft "Guidance for Industry – Labeling for Combined Oral Contraceptives." Our aim is simply to assist the FDA in its efforts to provide the most accurate and up-to-date information to women and their health care providers.

Sincerely,

Susan Wysocki, RNC, NP, FAANP
President and CEO

[36] Lancet 355: 576-577